Comment on Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline Summary

To the Editor:

The article entitled "Medication-Related Osteonecrosis of the Jaw: MASSC/ISOO/ASCO Clinical Practice Guideline" was recently published by Yarom et al[1] and was summarized by Shapiro et al.[2] The Multinational Association of Supportive Care in Cancer (MASSC), the International Society of Oral Oncology (ISOO), and ASCO are to be commended for their effort to establish a multidisciplinary expert panel and formulate shared guidelines, with the aim of ensuring best practices for prevention and management of medication-related osteonecrosis of the jaw (MRONJ) in patients who receive bone-modifying agents (BMAs) for oncologic indications.

A systematic review was conducted to select founding articles and assign level of evidence and grade recommendations. The authors' statement that "formal quality assessment of included studies was not conducted" makes it difficult for the reader to understand the process of article selection and increases the risk of biases. Despite the insufficient evidence, their effort to summarize and coordinate the roles of different health care professionals (oncologist/hematologist, dental practitioners, and dental specialists) involved with patients who have metastatic cancer before, during, and after treatment with BMAs is sound. But some conclusions seem controversial and are highly debated in the literature.

First, the MASCC/ISOO/ASCO panel decided to adopt the running definition of disease proposed in the latest version of the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on MRONJ,[3] which is based on the presence of probing bone fistulas or frank bone exposure in the maxillofacial region persisting for longer than 8 weeks. Several observational studies,[4-10] reviews, and expert opinions[11-19] increased attention on the relatively common observation of patients who are receiving BMAs and who present with clinical signs other than probing bone fistula or frank bone exposure (ie, dentally unexplained pain or gum swelling, tooth mobility/loss, numbness of the lips or chin, mandible fracture). These possible nonexposed MRONJ patients are still excluded from the definition of an MRONJ patient, and they contribute to the perceived underestimation of the disease burden.[18,19]

In several recently published randomized controlled trials comparing the efficacy of denosumab and zoledronic acid in the cancer setting, a consistent number of patients receiving BMAs developed signs and symptoms that are compatible with exposed or nonexposed MRONJ during the study (ie, "potential" MRONJ patients),[20-24] of whom only a few were confirmed by the adjudication committees, based on the AAOMS 2009 and 2014 definitions[3] (Table 1). Unfortunately, neither clinical nor radiologic data for patients who were not adjudicated have been reported so far. Thus, there is an urgent need to expand the definition of an MRONJ patient to encompass the other manifestations of nonexposed MRONJ.

Likewise the restricted and purely clinical definition of an MRONJ patient that was adopted and the recommended clinical staging system[1-3] are questionable, because they confine patients with nonexposed MRONJ symptoms into a kind of preclinical disease stage (stage 0) that might delay diagnosis and the start of appropriate treatments.

The Expert Panel on MRONJ of the Italian Societies of Maxillofacial Surgery and Oral Pathology and Medicine have proposed and implemented the inclusion of imaging findings in the diagnostic work-up and staging of disease,[14,25-27] on the assumption that MRONJ is definitely a bone disease. Despite the emerging role of computed tomography (CT) in the early recognition of MRONJ and definition of the extent of bone disease,[6-10,28-32] the MASCC/ISOO/ASCO panel does not formally recommend the use of imaging because it "may lead to an overestimate of true disease frequency." In contrast, we encourage the addition of imaging to exclude dental and bone diseases with similar clinical manifestations (ie, dental and periodontal disease, osteomyelitis, jawbone malignancies), because it would likely reduce the number of false positives (ie, patients who have nonspecific clinical signs of MRONJ but who do not have the disease) and favor diagnosis of patients who have nonexposed symptoms but who show bone involvement at CT scan. The adoption of a broader definition of MRONJ that is based on the coexistence of clinical (including the nonexposed variant) and radiologic signs is clearly needed.[14,19]

Originally, overt bone exposure was the only clinical determinant of MRONJ, and the prerequisite of 8-week observation to confirm the initial suspicion was suitable.[1-3] Because probing bone fistulas have also become a major sign of MRONJ, 8-week observation might be pointless, because it is known that untreated mucosal fistula arising from dental foci may persist much longer if left untreated. Instead, the use of x-rays and CT scans would add to the diagnostic process and accelerate the final diagnosis.

The authors' recommendation to "avoid elective dentoalveolar surgical procedures (eg, nonmedically

TABLE 1. Patients With Potential or Adjudicated MRONJ in Randomized Trials

First Author	Disease Type	No. of Patients	Patients With MRONJ			
			Potential		Adjudicated	
			No.	%	No.	%
Saad[20]	Solid tumors	5,723	287	5.0	89	1.6
Stopeck[21]	Breast and prostate cancer (prolonged therapy)	3,920	341[a]	8.6	140[b]	3.5
Raje[22-24]	Myeloma	1,718	158	9.2	59	3.4

Abbreviation: MRONJ, medication-related osteonecrosis of the jaw.

[a]Patients with breast cancer: 119 receiving denosumab only, 93 receiving zoledronic acid and then denosumab. Patients with prostate cancer: 75 receiving denosumab only, 54 receiving zoledronic acid and then denosumab.

[b]Patients with breast cancer: 48 receiving denosumab only, 35 receiving zoledronic acid and then denosumab. Patients with prostate cancer: 36 receiving denosumab only, 21 receiving zoledronic acid and then denosumab.

necessary extractions, alveoloplasties, and implants) during BMA treatment at oncologic doses"[1,2] and the statement "exceptions may be considered" based on a risk-benefit ratio are generally agreeable. Nevertheless, it would be useful to clarify what "non medically necessary extractions" refers to and to emphasize the role of tooth extraction as an established risk reduction strategy to be implemented not just before but also during active treatment with BMAs at oncologic doses.

Despite the fact that trauma and tooth extraction have long been considered the main trigger of MRONJ, in recent years, the role of local infection in the pathogenesis of osteonecrosis has become more convincing.[19,33-35] In fact, dental and periodontal infections are likely to propagate to the underlying alveolar bone, which has been altered by BMAs and cannot properly react; thus, osteonecrosis of the jaw might develop well before it is clinically detectable.[36] For example, in a recent trial of denosumab and zoledronic acid in patients with myeloma (only patients without pre-existing severe dental problems were included),[22] most of the MRONJ adjudicated cases (32 of 49) were observed during a relatively short time after somewhat unexpected dental procedures (unspecified regarding type and reason).[22-24] In this scenario, early surgical tooth extraction of compromised teeth with alveoloplasty and flap closure is a reasonable strategy to prevent MRONJ occurrence during BMA treatment.[19,33,35-37] It should be made clear that delaying the extraction of compromised teeth would be detrimental to patients and expose them to an increased risk of MRONJ.

Finally, we argue against the authors' recommendation that nonsurgical treatment should be favored in the initial stages of MRONJ and that using aggressive surgical interventions should be limited to more advanced and compromised conditions.[1,2] The limited evidence and lack of robust data on treatment of MRONJ has led the clinical community to adopt the prudent approach that conservative treatments, being less invasive, should be preferred over surgical therapy. Yet, there is a growing body of knowledge that surgery performs better than conservative treatments in all stages of disease, in terms of both symptom control and disease resolution.[19,34-45] Anticipating surgical treatment for the initial stages of MRONJ would reduce the aggressiveness of surgery on patients and increase the chance of cure and long-term control. On the contrary, nonsurgical therapies might be conceivable when surgery is contraindicated or declined and symptomatic improvement is the only purpose of treatment. We hope that these observations will help improve the quality of life for patients with cancer and myeloma who are receiving BMAs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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